Appendix 3: Forest plots, timing of ART in TB/HIV

Comparison A is ART <= 2 weeks after TB treatment compared to ART > 2 weeks and <= 8 weeks after TB treatment. Four studies using ART timepoints that permitted this comparison. Comparison B is ART <= 4 weeks after TB treamtent compared to ART > 4 weeks after TB treatment.

Three studies (Amogne, SAPiT and TIME) had data disaggregated by CD4 count, two studies (RAFA and TB-HAART) only included people with CD4 counts > 50 cells/mm3, two further studies (CAMELIA and STRIDE) provided some CD4-disaggregated data directly from authors.

Note that Amogne et al is a study that used three timepoints (1 week, 4 weeks and 8 weeks). For comparison A the 4 weeks and 8 week groups are combined ("Amogne 1vs4and8"), for comparison B the 1 and 4 week groups are combined ("Amogne 1and4vs8").

The SAPiT trial initially randomised people into three arms (4 weeks, 8-12 weeks and 26 weeks). The 26 week group was stopped early due to signal of harm. SAPiT data are reported in two primary manuscripts, one comparing combined 4 and 8-12 weeks group to 26 weeks group and one comparing 4 and 8-12 weeks groups to each other. All SAPiT data in these meta-analyses pertain to the comparison of 4 weeks vs. 8-12 weeks (2011 NEJM paper).

Not all studies disaggregated data by CD4 criteria and some studies allowed disaggregation of some outcomes but not others, so the graphs of low CD4 (<= 50 cells) and higher CD4 (> 50 cells) do not represent all the available data (THIRST and Sinha et al do not have any CD4 disaggregated data and so are not present in analyses by CD4 strata),

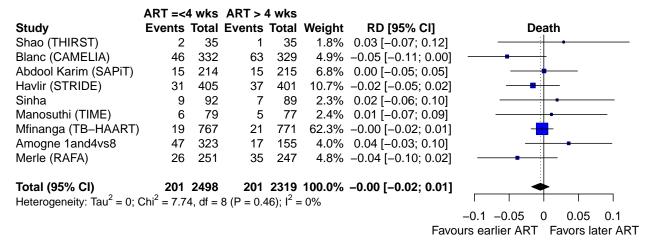
All summary estimates summary estimates are from random effects meta-regression models using package 'meta' in R statistical software.

Death

All CD4 counts

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks Study **Events Total Events Total Weight** RD [95% CI] Death Shao (THIRST) 2 35 35 17.3% 0.03 [-0.07; 0.12] Blanc (CAMELIA) 46 332 63 329 29.0% -0.05 [-0.11; 0.00] Amogne 1vs4and8 27 163 37 315 25.1% 0.05 [-0.02; 0.12] Merle (RAFA) 26 251 35 247 28.6% -0.04 [-0.10; 0.02] Total (95% CI) 101 781 136 926 100.0% -0.01 [-0.06; 0.04] Heterogeneity: $Tau^2 = 0.0014$; $Chi^2 = 6.61$, df = 3 (P = 0.09); $I^2 = 55\%$ -0.1 -0.050 0.05 Favours earlier ART Favors later ART



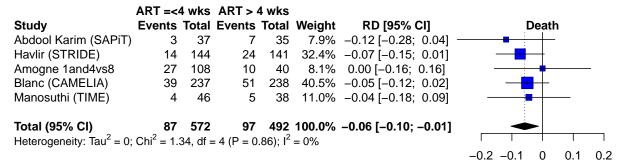
Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks

Study	Events	Total	Events	Total	Weight	RD [95% CI]	Death
Amogne 1vs4and8	16	59	21	89	21.9%	0.04 [-0.11; 0.18]	
Blanc (CAMELIA)	39	237	51	238	78.1%	-0.05 [-0.12; 0.02]	
Total (95% CI) Heterogeneity: Tau ²						-0.03 [-0.10 ; 0.04] = 8%	
							-0.15 -0.05 0 0.05 0.1 0.15

Favours earlier ART Favors later ART

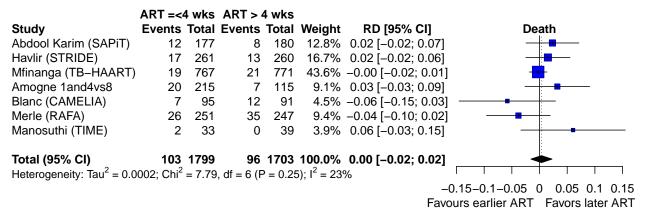
Comparison B (ART <=4 weeks vs. ART > 4 weeks)



Favours earlier ART Favors later ART

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

	ART = < 3	2 wks	ART 2-	8 wks			
Study	Events	Total	Events	Total	Weight	RD [95% CI]	Death
Amogne 1vs4and8	11	104	16	226	34.2%	0.03 [-0.03; 0.10]	:
Blanc (CAMELIA)	7	95	12	91	25.4%	-0.06 [-0.15; 0.03]	
Merle (RAFA)	26	251	35	247	40.3%	-0.04 [-0.10; 0.02]	
Total (95% CI)		450	63	564	100.0%	-0.02 [-0.07; 0.04]	
Heterogeneity: Tau ² :	= 0.0010;	Chi ² =	3.64, df =	= 2 (P =	= 0.16); I ²	= 45%	
							-0.1 -0.05 0 0.05 0.1
						Favo	urs earlier ART Favors later ART

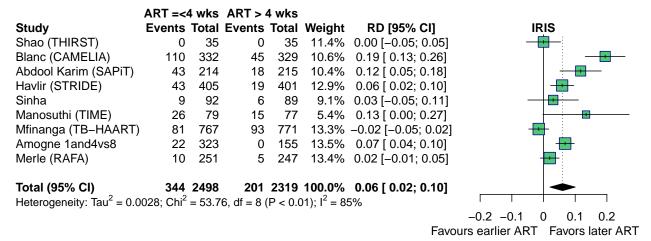


IRIS

All CD4 counts

Comparison A (ART <= 2 weeks vs. ART > 2 weeks and <= 8 weeks)

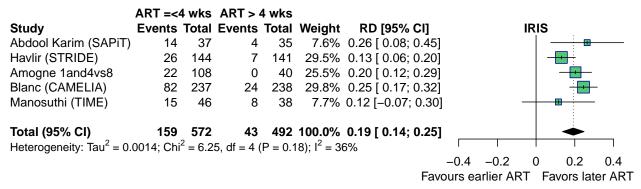
	ART =<	2 wks	ART 2-	8 wks			
Study	Events	Total	Events	Total	Weight	RD [95% CI]	IRIS
Shao (THIRST)	0	35	0	35	24.7%	0.00 [-0.05; 0.05] -
Blanc (CAMELIA)	110	332	45	329	24.1%	0.19 [0.13; 0.26	-
Amogne 1vs4and8	16	163	6	315	25.1%	0.08 [0.03; 0.13	
Merle (RAFA)	10	251	5	247	26.1%	0.02 [-0.01; 0.05] =
Total (95% CI) Heterogeneity: Tau ² =	136 = 0.0095:	781 Chi ² =	56 53.76. df	926 = 3 (P	100.0% < 0.01): I	0.07 [–0.03; 0.17 ² = 94%	1
. reteregement, rau	0.0000,	•	001. 0, 0.	٠ (.	, .	0.70	-0.2 -0.1 0 0.1 0.2
						Fa	ours earlier ART Favors later ART



Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks Study Events Total Events Total Weight RD [95% CI] **IRIS** Amogne 1vs4and8 24.8% 0.20 [0.08; 0.33] 16 59 6 89 Blanc (CAMELIA) 82 237 238 75.2% 0.25 [0.17; 0.32] 24 30 327 100.0% 0.23 [0.17; 0.30] Total (95% CI) 98 296 Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0$ % -0.3 - 0.2 - 0.1 0 0.1 0.2 0.3 Favours earlier ART Favors later ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)



NB. For Blanc 2011 (CAMELIA) trial, CD4 count groupings of incident IRIS are based on baseline CD4 count, not screening CD4 count. For Amogne et al (2015) counts by CD4 categories calculated from the supplementary data file provided with manuscript.

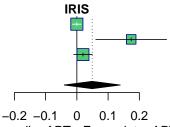
Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART	=<2	wks	ART	2-8	wks
-----	-----	-----	-----	-----	-----

Study	Events	Total	Events	Total	Weight	RD [95% CI]
Amogne 1vs4and8	0	104	0	226	38.6%	0.00 [-0.01; 0.01]
Blanc (CAMELIA)	28	95	11	91	24.0%	0.17 [0.06; 0.29]
Merle (RAFA)	10	251	5	247	37.4%	0.02 [-0.01; 0.05]

Total (95% CI) 38 450 16 564 100.0% 0.05 [-0.04; 0.14]

Heterogeneity: $Tau^2 = 0.0054$; $Chi^2 = 41.93$, df = 2 (P < 0.01); $I^2 = 95\%$



Favours earlier ART Favors later ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)

	ART =<	4 wks	ART >	4 wks		
Study	Events	Total	Events	Total	Weight	RD [95% CI]
Abdool Karim (SAPiT)	29	177	14	180	11.6%	0.09 [0.02; 0.15]
Havlir (STRIDE)	17	261	12	260	17.6%	0.02 [-0.02; 0.06]
Mfinanga (TB-HAART)	81	767	93	771	19.5%	-0.02 [-0.05; 0.02]
Amogne 1and4vs8	0	215	0	115	23.1%	0.00 [-0.01; 0.01]
Blanc (CAMELIA)	28	95	11	91	5.9%	0.17 [0.06; 0.29]
Merle (RAFA)	10	251	5	247	19.9%	0.02 [-0.01; 0.05]
Manosuthi (TIME)	11	33	7	39	2.3%	0.15 [-0.05; 0.35]

Total (95% CI) 176 1799 142 1703 100.0% 0.03 [0.00; 0.06]

Heterogeneity: $Tau^2 = 0.0011$; $Chi^2 = 25.88$, df = 6 (P < 0.01); $I^2 = 77\%$

-0.3-0.2-0.1 0 0.1 0.2 0.3

IRIS

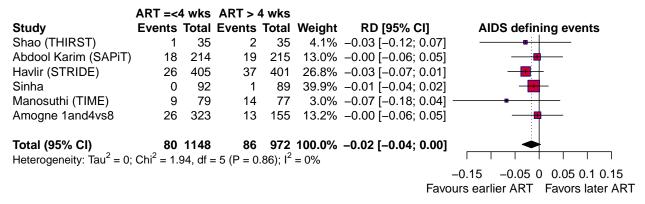
Favours earlier ART Favors later ART

Aids Defining Events

All CD4 counts

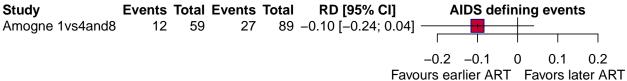
Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

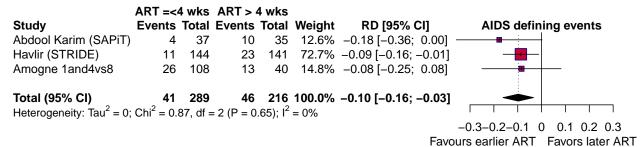
ART =<2 wks ART 2-8 wks AIDS defining events Study **Events Total Events Total Weight** RD [95% CI] Shao (THIRST) 1 35 2 35 22.2% -0.03 [-0.12; 0.07] Amogne 1vs4and8 12 163 27 315 77.8% -0.01 [-0.06; 0.04] Total (95% CI) 13 198 29 350 100.0% -0.02 [-0.06; 0.03] Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0\%$ -0.1 -0.050 0.05 0.1 Favours earlier ART Favors later ART



Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks





Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks

Study	Events	Total	Events	Total	RD [95% CI]	AIDS defir	ning events
Amogne 1vs4and8	0	104	0	226	0.00 [-0.01; 0.01]		
					Favo		0 0.005 0.01 Favors later ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)

ART =<4 wks ART > 4 wks

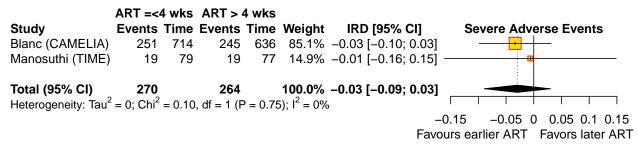
Study	Events	Total	Events	Total	Weight	RD [95% C		AIDS d	efining e	events
Abdool Karim (SAPiT)	14	177	9	180	14.2%	0.03 [-0.02; 0	0.08]	-	- : -	-
Havlir (STRIDE)	15	261	14	260	21.5%	0.00 [-0.04; 0	0.04]		•	
Amogne 1and4vs8	0	215	0	115	64.3%	0.00 [-0.01; 0	0.01]			
Total (95% CI)	29	653	23	555	100.0%	0.00 [-0.02; (0.03]			=
Heterogeneity: $Tau^2 = 0$.	0001; Ch	$i^2 = 2.9$	1, df = 2 ((P = 0.2)	23); $I^2 = 3^{\circ}$	1%				
								-0.05	0	0.05
							Favou	rs earlier A	RT Fav	ors later ART

Serious Adverse Events

Note that Serious Adverse Events (SAEs) have very different definitions in each study and comparisons may not be meaningful. Some studies include IRIS and AIDS defining events as SAEs, whilst others don't. Most studies report total numbers of SAEs, not whether an individual person had an SAE or not (ie. a single person can have more than one SAE). One study (Amogne) only reports hepatoxicity and not other SAEs.

This meta-analysis is only for the two studies that specifically report **treatment assosciated** SAEs and considers incidence of treatment-related serious adverse events by per person-years of observation.

All CD4 counts



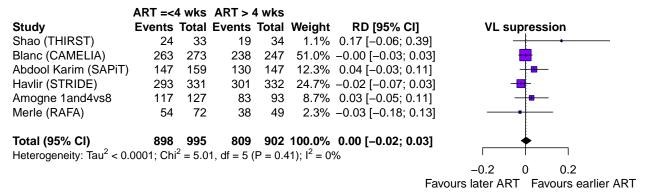
VL supression

All CD4 counts

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

	ART =<	2 wks	ART 2-	8 wks			
Study	Events	Total	Events	Total	Weight	RD [95% CI]	VL supression
Shao (THIRST)	24	33	19	34	3.5%	0.17 [-0.06; 0.39	<u> </u>
Blanc (CAMELIA)	263	273	238	247	65.3%	-0.00 [-0.03; 0.03	B] 📅
Amogne 1vs4and8	50	53	150	167	23.9%	0.05 [-0.03; 0.12] •
Merle (RAFA)	54	72	38	49	7.3%	-0.03 [-0.18; 0.13	B] — • •
Total (95% CI)	391	431	445	497	100.0%	0.01 [-0.03; 0.06]
Heterogeneity: Tau ² :	= 0.0005;	Chi ² =	3.70, df =	= 3 (P =	= 0.30); I ²	= 19%	
							-0.2 0 0.2
						F	avours later ART Favours earlier ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)



Denominator is all those who had VL measured, not all those randomised.

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks

 Study
 Events
 Total
 Events
 Total
 RD [95% CI]
 VL supression

 Amogne 1vs4and8
 16
 16
 40
 41
 0.02 [-0.07; 0.12]
 -0.1 -0.05
 0
 0.05
 0.1

 Favours later ART Favours earlier ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)

ART =<4 wks ART > 4 wks

Events Total Events Total Weight Study RD [95% CI] VL supression Abdool Karim (SAPiT) 30 32 23 38.0% 0.09 [-0.07; 0.24] 27 Amogne 1and4vs8 36 37 20 20 62.0% -0.03 [-0.12; 0.06] Total (95% CI) 69 47 100.0% 0.02 [-0.11; 0.14] 66 43 Heterogeneity: $Tau^2 = 0.0048$; $Chi^2 = 2.13$, df = 1 (P = 0.14); $I^2 = 53\%$ -0.2 -0.10 0.1 0.2 Favours later ART Favours earlier ART

Denominator is all those who had VL measured, not all those randomised.

High CD4 counts (CD4 > 50)

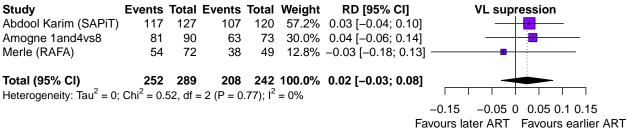
Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks

Study **Events Total Events Total Weight** RD [95% CI] VL supression Amogne 1vs4and8 110 126 68.0% 0.05 [-0.06; 0.15] 34 37 Merle (RAFA) 54 72 32.0% -0.03 [-0.18; 0.13] 38 49 148 175 100.0% 0.02 [-0.06; 0.11] Total (95% CI) 88 109 Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.65$, df = 1 (P = 0.42); $I^2 = 0$ % -0.05 0 0.05 0.1 0.15 -0.15Favours later ART Favours earlier ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)

ART =<4 wks ART > 4 wks



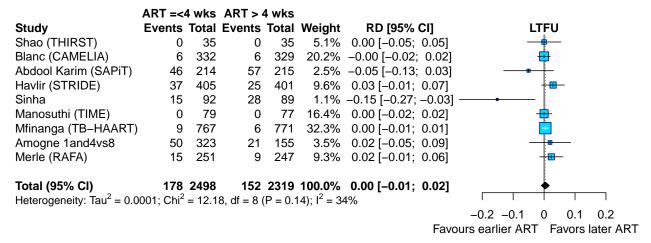
Denominator is all those who had VL measured, not all those randomised.

Loss to follow up (LFTU)

All CD4 counts

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

	ART =<	2 wks	ART 2-	8 wks				
Study	Events	Total	Events	Total	Weight	RD [95% CI]	LT	FU
Shao (THIRST)	0	35	0	35	9.3%	0.00 [-0.05; 0.05]		
Blanc (CAMELIA)	6	332	6	329	65.5%	-0.00 [-0.02; 0.02]		-
Amogne 1vs4and8	26	163	45	315	5.8%	0.02 [-0.05; 0.08]	-	 •
Merle (RAFA)	15	251	9	247	19.3%	0.02 [-0.01; 0.06]	_	
Total (95% CI)						0.01 [-0.01; 0.02]		
Heterogeneity: Tau ²	= 0; Chi ² :	= 1.80,	df = 3 (P	= 0.62); $I^2 = 0\%$		ı	1
							-0.05	0.05
						Favou	rs earlier ART	Favors later ART



Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks

Events Total Events Total RD [95% CI] LTFU Study Amogne 1vs4and8 10 59 12 89 0.03 [-0.08; 0.15] -0.15-0.1-0.05 0 0.05 0.1 0.15

Favours earlier ART Favors later ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)

ART =<4 wks ART > 4 wks

Events Total Events Total Weight RD [95% CI] Study Amogne 1and4vs8 17 108 5 40 12.2% 0.03 [-0.09; 0.16] Manosuthi (TIME) 0 46 0 38 87.8% 0.00 [-0.05; 0.05] Total (95% CI) 17 154 5 78 100.0% 0.00 [-0.04; 0.05] Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.70$, df = 1 (P = 0.40); $I^2 = 0$ % -0.15-0.1-0.05 0 0.05 0.1 0.15

Favours earlier ART Favors later ART

High CD4 counts (CD4 > 50)

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

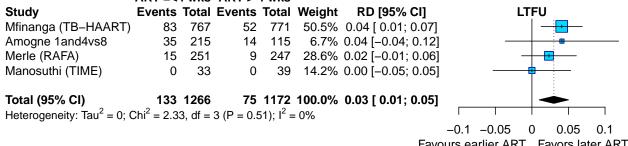
ART =<2 wks ART 2-8 wks

Study Events Total Events Total Weight RD [95% CI] **LTFU** Amogne 1vs4and8 17 104 32 226 16.5% 0.02 [-0.06; 0.11] 9 247 83.5% 0.02 [-0.01; 0.06] Merle (RAFA) 15 251 Total (95% CI) 32 355 41 473 100.0% 0.02 [-0.01; 0.06] Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$ 0.05 -0.1 -0.050.1 0

Favours earlier ART Favors later ART

Comparison B (ART <=4 weeks vs. ART > 4 weeks)

ART =<4 wks ART > 4 wks



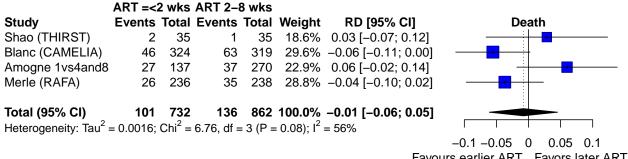
Favours earlier ART Favors later ART

Death (sensitivity analysis)

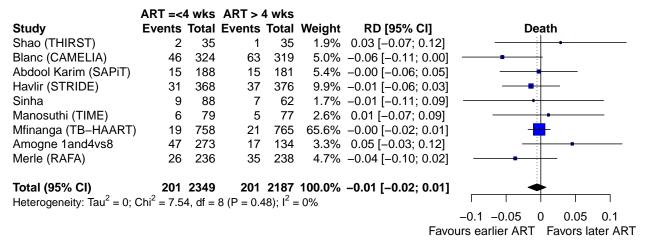
Sensitivity analysis, where denominator is all those with ascertained outcome (ie. excluding those LTFU)

All CD4 counts

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)



Favours earlier ART Favors later ART



Study

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<	2 wks	ART	2-8	wks
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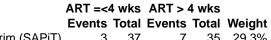
7111 - 42 WAO 7111 Z O WAO												
Study	Events	Total	Events	Total	Weight	RD [95% CI]		Dea	ath			
Amogne 1vs4and8	16	59	21	89	100.0%	0.04 [-0.11; 0.18]	٠				—	
Blanc (CAMELIA)	39		51		0.0%							
Total (95% CI)						0.04 [-0.11; 0.18]	l				_	
Heterogeneity: Tau ² =	= NA; Chi	$^{2} = 0.0$	0, df = 0	P = NA	$A); I^2 = NA$	۸%					l	
							-0.15	-0.050	0.05	0.1 0.	15	
						Fav	Ours Aai	lior ΔRT	Favor	e later	ΔRT	

RD [95% CI]

Favours earlier ART Favors later ART

Death

Comparison B (ART <=4 weeks vs. ART > 4 weeks)



Abdool Karim (SAPiT) 3 37 7 35 29.3% -0.12 [-0.28; 0.04] -Havlir (STRIDE) 14 24 0.0% Amogne 1and4vs8 27 108 10 40 30.0% 0.00 [-0.16; 0.16] Blanc (CAMELIA) 39 51 0.0% Manosuthi (TIME) 46 5 38 40.7% -0.04 [-0.18; 0.09] 4

Total (95% CI) 87 191 97 113 100.0% -0.05 [-0.14; 0.03]

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.14$, df = 2 (P = 0.56); $I^2 = 0$ %

Comparison A (ART <=2 weeks vs. ART >2 weeks and <=8 weeks)

ART =<2 wks ART 2-8 wks Study **Events Total Events Total Weight RD [95% CI]** Death Amogne 1vs4and8 11 104 16 226 47.5% 0.03 [-0.03; 0.10] Blanc (CAMELIA) 7 12 0.0% Merle (RAFA) 26 236 35 238 52.5% -0.04 [-0.10; 0.02] 63 464 100.0% -0.00 [-0.07; 0.07] Total (95% CI) 44 340 Heterogeneity: $Tau^2 = 0.0016$; $Chi^2 = 2.45$, df = 1 (P = 0.12); $I^2 = 59\%$ -0.1 -0.050 0.05 0.1 Favours earlier ART Favors later ART

